



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/57, 31/675, 38/13, 31/52	A1	(11) International Publication Number: WO 95/34306 (43) International Publication Date: 21 December 1995 (21.12.95)
(21) International Application Number: PCT/EP95/02289 (22) International Filing Date: 13 June 1995 (13.06.95) (30) Priority Data: 110011 13 June 1994 (13.06.94) IL (71) Applicant (for all designated States except US): YEDA RE- SEARCH AND DEVELOPMENT CO., LTD. AT THE WEIZMANN INSTITUTE OF SCIENCE [IL/IL]; P.O. Box 95, 76100 Rehovot (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): SHINITZKY, Meir [IL/IL]; 20 Derech Haganim Street, 46910 Kfar Shmaryahu (IL). DECKMANN, Michael [DE/FR]; 24, rue de Kreutzberger, F-68500 Guebwiller (FR). (74) Agent: GRÜNECKER, KINKELDEY, STOCKMAIR & PARTNER; Maximilianstrasse 58, D-80538 München (DE).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: USE OF IMMUNOSUPPRESSIVE AGENTS FOR THE TREATMENT OF SCHIZOPHRENIA		
(57) Abstract The invention relates to a pharmaceutical composition for the treatment of schizophrenic disorders which comprises a pharmaceutically acceptable carrier and as active ingredient an immunosuppressive agent.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Use of immunosuppressive agents for the treatment of schizophrenia

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to the use of immunosuppressive agents for the treatment of schizophrenic disorders.

The schizophrenic disorders, as defined by DSM-III (the American Psychiatric Association's Diagnostic and Statistical Manual, 3rd edition) are mental disorders with a tendency towards chronicity which impairs functioning and which is characterized by psychotic symptoms involving disturbances of thinking, feeling and behavior.

Schizophrenia occurs worldwide. Although it is one of the most severe and prevalent mental disorders of well documented symptomatology and has been extensively investigated over the past decades, the etiology of this disease is still an enigma. Schizophrenic patients are mainly treated by chemotherapy with antipsychotic drugs, such as the neuroleptic drugs haloperidol and chlorpromazine. Electroconvulsive therapy is also used in some cases. However, individual response to each drug varies, and both chemotherapy and electroconvulsive therapy are not successful for many schizophrenic patients.

A series of biochemical findings have suggested that autoimmune elements might be implicated in the etiology of schizophrenia¹⁻⁶. We recently detected autoimmune antibodies on platelets from schizophrenic patients which block dopamine uptake and cross-react with brain tissue^{4,6}. In line with the

hypothesis that autoimmune reaction against the dopamine receptor takes place in schizophrenia⁷, we have further suggested that the onset of the schizophrenia may stem from binding of platelet autoantibodies to one of the dopamine receptors in the central nervous system (CNS)^{4,6}. However, the assumption that schizophrenia is an autoimmune disease has not been definitely ascertained as yet.

SUMMARY OF INVENTION

It has now been found in accordance with the present invention that mental patients with severe chronic schizophrenia, who did not respond to conventional treatments, may be successfully treated with azathioprine, a drug commonly used for autoimmune and inflammatory diseases. Treatment of patients has resulted in a remarkable improvement in the psychiatric state which correlated with a marked reduction in platelet-associated autoantibodies (PAA).

The present invention thus relates to pharmaceutical compositions for the treatment of schizophrenic disorders comprising as active ingredient an immunosuppressive agent together with a pharmaceutically acceptable carrier.

The invention further relates to the use of an immunosuppressive agent for the manufacture of pharmaceutical compositions for the treatment of schizophrenic disorders.

In another embodiment the invention relates to a method of treatment of a schizophrenic patient which comprises administering to a patient in need thereof an effective amount of an immunosuppressive agent.

Any immunosuppressive agent may be used according to the invention. Among known immunosuppressive drugs that might be used in the invention are prednisone, methylprednisolone, azathioprine, cyclophosphamide and cyclosporine. In a preferred embodiment, azathioprine is used.

The choice of the immunosuppressive agent, mode of administration, dosage and duration of the treatment will depend on the patient's individual response, his age, and severity of the disease. If necessary, a combination of two different immunosuppressive agents may be used.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A-B show 28-week scores of a schizophrenic patient during and after azathioprine treatment, as described in Example 1, wherein Fig. 1A shows scores of level of platelet-associated autoantibodies (PAA) presented in units of optical density (O.D.) per 10^8 platelets in 1 ml; and Fig. 1B shows scores of psychiatric condition by the positive and negative syndrome scale (PANSS): empty circles - positive syndrome scale; filled circles - negative syndrome scale; empty squares - general psychopathological scale; filled squares, summation of 3 scales.

Figs. 2A-B show 14-week scores of a schizophrenic patient during and after azathioprine treatment, as described in Example 2, wherein Fig. 2A shows scores of PAA and Fig. 2B shows scores of psychiatric conditions by PANSS, as defined in Fig. 1.

Figs. 3A-B show 25-week scores of a schizophrenic patient during and after azathioprine treatment, as described in Example 3, wherein Fig. 3A shows scores of PAA and Fig. 3B shows scores of psychiatric conditions by PANSS, as defined in Fig. 1.

DESCRIPTION OF THE INVENTION

According to the present invention, schizophrenic patients that did not respond to, or showed only limited response to, neuroleptics, were treated with immunosuppressant drugs.

The treatment consisted of three consecutive periods, in which the daily dose of azathioprine first raised from 50 mg to 150 mg, then remained at a constant dose in the second period, and then was gradually tapered and terminated in the third period. The patients remained on treatment with other antipsychotic drugs, such as clothiapine and lithium.

The results of the treatment were followed by the PAA profile and the PANSS psychiatric ratings, as shown in the following non-limiting examples and figures.

EXAMPLES

EXAMPLE 1.

A female patient, V.J., age 52, suffered from paranoid schizophrenia since the age of 25. At the age of 32 she was diagnosed as suffering from systemic lupus erythematosus (SLE), followed by hypothyroidism of unknown etiology. Until the age of 45 she was hospitalized several times due to

eruptions of psychotic episodes of paranoid symptomology. She was then diagnosed as suffering from paranoid schizophrenia according to the DSM III verified later by the DSM III-R. Since the age of 46 she is permanently hospitalized in a Psychiatric Hospital. She had frequent psychotic episodes, manifested by bizarre paranoid thoughts accompanied by command hallucinations, extreme psychomotor agitation and total self neglect. Partial apparent remissions lasted for a few weeks only. During the 5 years prior to the present treatment, she was treated with various neuroleptics, lithium and electroconvulsive therapy with only limited response, in addition to prednisone (30 mg/daily) for SLE, and thyroxine (100-150 μ g/daily) for hypothyroidism.

A therapeutic regimen with the immune suppressant azathioprine was instituted for the patient, during which her psychiatric condition was assessed by the positive and negative syndrome scale (PANSS) for schizophrenia^{9,10}. This scale assesses positive symptoms (delusions, hallucinations etc.) and negative symptoms (blunt affect, emotional withdrawal, etc.) and general psychopathological characteristics. The PANSS has a good inter and intra-rater reliability and has been widely used for psychiatric assessment in various clinical studies^{9,10}.

The treatment consisted of 3 consecutive periods during which the patient remained on clothiapine (80 mg daily) and lithium (600 mg daily) treatment. In the first (an adjustment of 8 weeks), the chronic steroid treatment (Meticorten, Schering) was gradually tapered from 30 mg/daily to 5

mg/daily, while azathioprine (Imuran™, Borroughs-Wellcome) was given orally starting from 50 mg/daily up to 150 mg/daily. In the second period (10 weeks), azathioprine was administered at a daily dose of 150 mg. During the third period (8 weeks) azathioprine treatment was gradually tapered down to termination. At the beginning of the trial the patient's laboratory values were: Sedimentation rate - 35/68; serum immunoglobulins - normal; haemoglobin - 11.0 gr/dl; white blood cell count - 5600 cmm, with a normal differentiation count and platelet count of 147,000/cmm. Some relevant "autoimmune" parameters were taken shortly before the treatment and 16 weeks after the beginning of the trial (i.e. 8 weeks within the second period). Thus, before treatment, serum C-Reactive Protein (CRP) was 30 mg/dl and rheumatoid factor 200 IU/ml. After treatment, these values returned to normal, while antinuclear factor was reduced from 2+ to 1+. At the same time, the platelet count rose from $147 \times 10^9/L$ to $260 \times 10^9/L$. These results clearly indicate that the immunosuppressive treatment reduced the production of some autoantibodies and of a major acute phase reactant. The platelet count almost doubled presumably due to a decrease in the titer of platelet-associated autoantibodies, PAA (see below).

At weekly intervals, PAA was assayed on freshly drawn peripheral blood, as previously described^{4,6}. A day or two later the PANSS psychiatric rating was performed by a different group uninformed about the PAA values.

The results of the PAA profile and the psychiatric ratings are shown in Figs. 1A and 1B. As shown, the PAA measurement at the beginning of the study (1.65 O.D. units) was over 3-fold higher than the normal cut off level (0.5 O.D. units). Already within the first trial period the PAA value was reduced and in the midst of the second period it reached normal values (Fig. 1A), fluctuating around the cut off level. Four weeks after terminating the azathioprine treatment, the PAA titer was again elevated and approached the initial level (see Fig. 1A).

The PANSS scorings at the beginning of the study were typical of a severe psychotic state. A small and probably insignificant reduction in PANSS scoring was noticed at the beginning of the second period of the trial. However, a marked improvement in PANSS scoring was recorded at the 6th week of the second period, which took place approximately one week after the PAA level entered into the normal range (Figs. 1A and 1B). The psychological improvement of the patient continued well into the third period (Fig. 1B) where the patient was essentially free of treatment. The PANSS ratings indicated a marked psychiatric improvement that followed the decrease in PAA but remained unchanged when the latter relapsed. Today the patient is practically in a state of remission (symptoms below the 25th percentile in the PANSS scale) and her appearance and social performance are close to normal.

A broad spectrum of examinations (data not shown) have clearly indicated that the observed effects could neither be

attributed to an anti-lupus action of azathioprine, nor to a non-specific steroid effect. It seems plausible, therefore, that in our case immunosuppression induced by azathioprine acted on a putative autoimmune arm of schizophrenia, which was associated with PAA. Along this avenue it might be proposed that after a lag time the action of these autoantibodies in the CNS is subsequently reduced to a level which is overtly manifested in the increase of mental competence (decrease in PANSS score). The ensued reduction in PAA antibodies in the CNS may have either directly alleviated the mental symptomatology or potentiated the therapeutic action of neuroleptics lithium.

The results of this case indicate a possible link between production of PAA and psychotic brain disturbances, and adds to the accumulating evidence that platelets and brain cells have antigenic cross reacting dopaminergic receptors. Based on this notion, and on the results presented here, new directions of research and treatment of mental disorders might be considered.

EXAMPLE 2.

A male patient, S.R., age 51, single, was diagnosed at the age of 24 as suffering from chronic paranoid schizophrenia which was mostly characterized by delusions and violence (physical). The patient did not respond to various neuroleptic treatments. During azathioprine treatment there was a significant improvement of his delusions and physical violence

alongside with improved insight to his illness. No adverse effects were recorded.

As shown in Figs. 2A and 2B, the PANSS scoring indicated a significant reduction in all parameters (improved psychological rating) in response to the treatment, which relapsed after termination of the treatment. PAA scoring indicated cycling and not much improvement.

EXAMPLE 3.

A male patient, P.M., age 41, single, was diagnosed as suffering from chronic paranoid schizophrenia for 23 years, characterized by delusions of reference and persecution and severe violence towards people and property. He did not respond to neuroleptics. There was slight but significant improvement with azathioprine treatment (a significant reduction in PANSS scoring). Blood count and biochemistry remained normal along the trial. PAA titer was normal in the middle of the treatment. The results are shown in Figs. 3A and 3B.

REFERENCES

1. Knight JG. Is schizophrenia an autoimmune disease? A Review. *Meth. Find. Exp. Clin. Pharmacol.* 1984; 6: 395-402.
2. Jankovic BD. From Immunoneurology to immunopsychiatry. Neuromodulating activity of antibrain antibodies. *Int. Rev. Neurobiol.* 1984; 26: 249-314.
3. DeLisi LE, Weber RJ, Pert CB. Are there antibodies against brain in sera from schizophrenic patients? *Biol. Psychiatry* 1985; 20: 94-119.
4. Shinitzky M., Deckmann M., Kessler A. et al. Platelet autoantibodies in dementia and schizophrenia - possible implication for mental disorders. *Ann. N.Y. Acad. Sci.* 1991; 621: 205-217.
5. Teplizki HA, Sela B, Shoenfeld Y. Autoantibodies to brain and polynucleotides in patients with schizophrenia: a puzzle. *Immunol. Res.* 1992; 11: 66-73.
6. Kessler A, Shinitzky M. Platelets from schizophrenic patients bear autoimmune antibodies which inhibit dopamine uptake. *Psychobiol.* 1993; 21: 299-306.
7. Abramsky O, Litvin Y. Autoimmune response to dopamine-receptor as a possible mechanism in the pathogenesis of Parkinson's disease and schizophrenia. *Perspect. Biol. Med.* 1978; 22: 104-114.
8. Leporrier M, Dighiero G, Auzemery M. Detection and quantification of platelet-bound antibodies with immunoperoxidase. *Br. J. Haematol.* 1979; 42: 605-611.

9. Kay SR, Puler LA, Eiszbein A. Positive and negative syndrome scale (PNASS). Toronto Multi-Heath Systems Inc. (1990).
10. Kay SR. Positive and negative syndromes in schizophrenia; Assessment and research. Bunner and Mazel Publishers, New York, 1991.

CLAIMS .

1. A pharmaceutical composition for the treatment of schizophrenic disorders which comprises a pharmaceutically acceptable carrier and as active ingredient an immunosuppressive agent.

2. A pharmaceutical composition according to claim 1 wherein the immunosuppressive agent is selected from prednisone, methylprednisolone, azathioprine, cyclophosphamide and cyclosporine.

3. A pharmaceutical composition according to claim 1 or 2 wherein the immunosuppressive agent is azathioprine.

4. Use of an immunosuppressive agent for the manufacture of a pharmaceutical composition for the treatment of schizophrenic disorders.

5. Use according to claim 4 wherein the immunosuppressive agent is selected from prednisone, methylprednisolone, azathioprine, cyclophosphamide and cyclosporine.

6. Use according to claim 4 or 5 wherein the immunosuppressive agent is azathioprine.

7. A method of treatment of a schizophrenic patient which comprises administering to said patient an effective amount of an immunosuppressive agent.

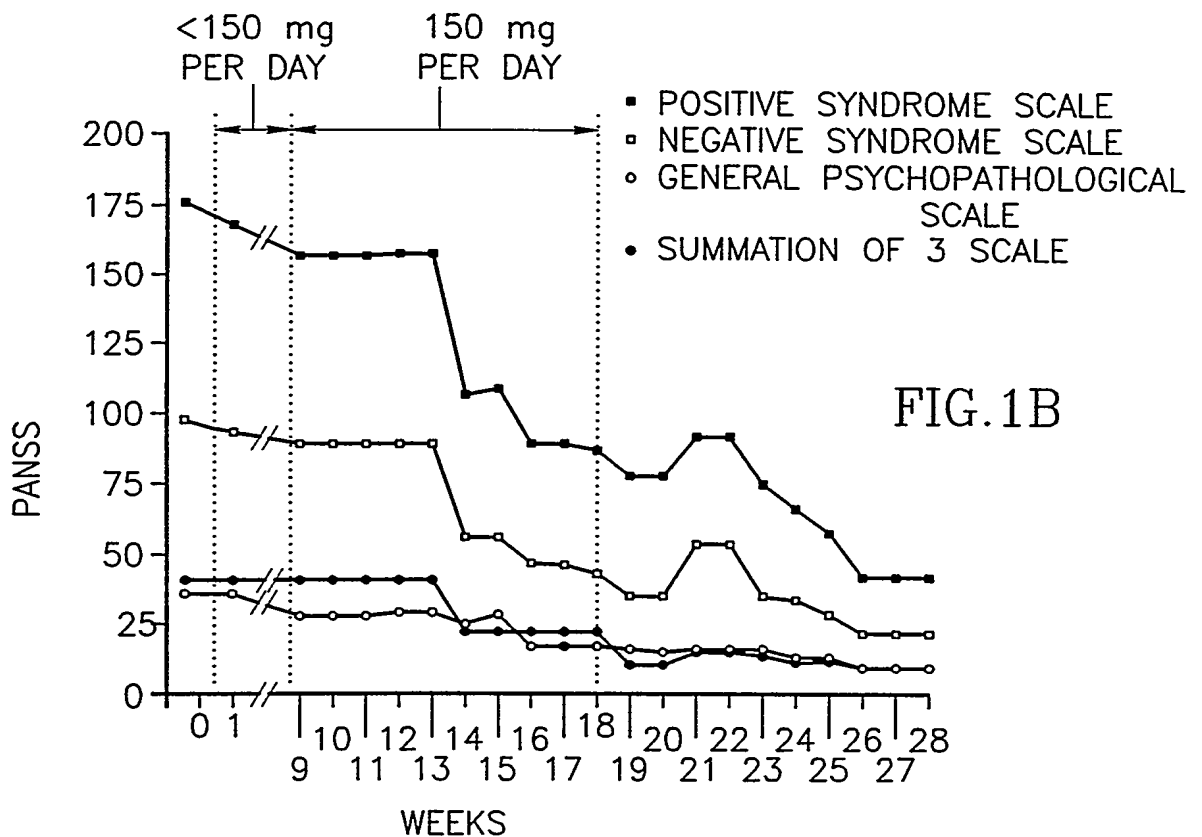
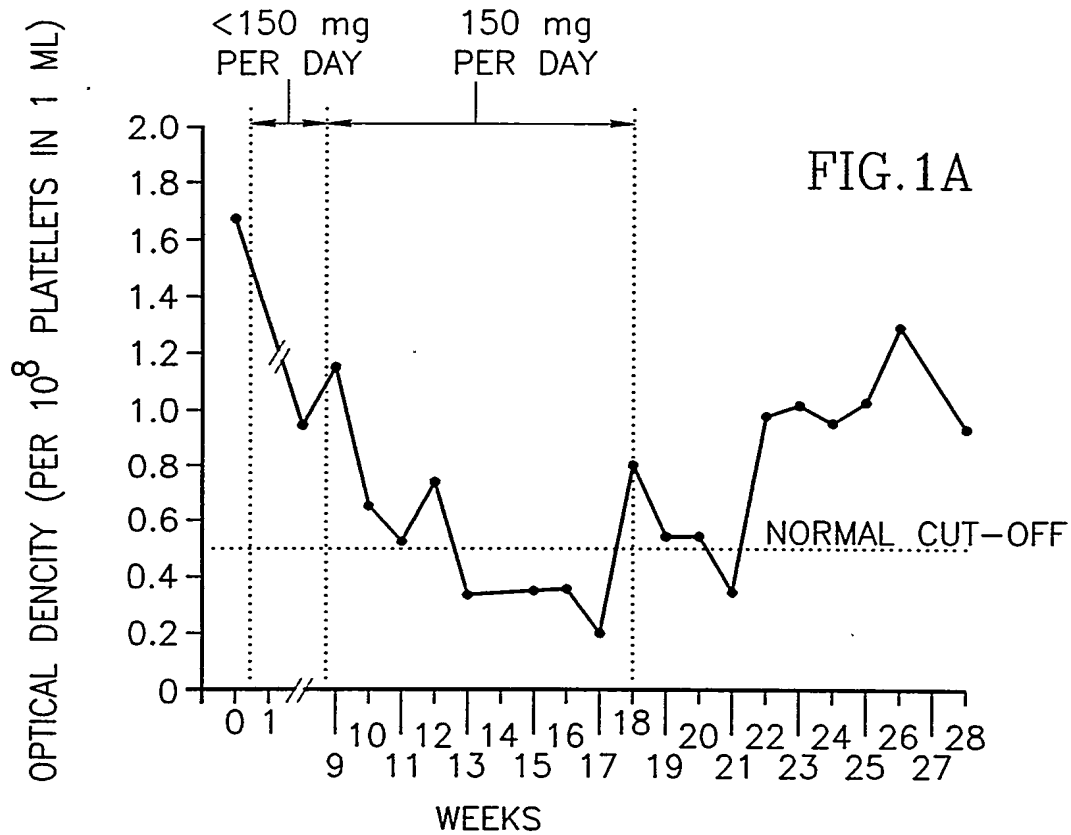
8. A method according to claim 7 wherein the immunosuppressive agent is selected from prednisone, methylprednisolone, azathioprine, cyclophosphamide and cyclosporine.

9. A method according to claim 7 or 8 wherein the immunosuppressive agent is azathioprine.

10. A method according to claim 7 wherein the patient is treated with a combination of 2 immunosuppressive agents.

11. A method according to claim 7 wherein the patient is maintained on treatment with antipsychotic drugs.

12. A method according to claim 11 wherein the immunosuppressive agent is azathioprine and the antipsychotic drugs are clothiapine and lithium.



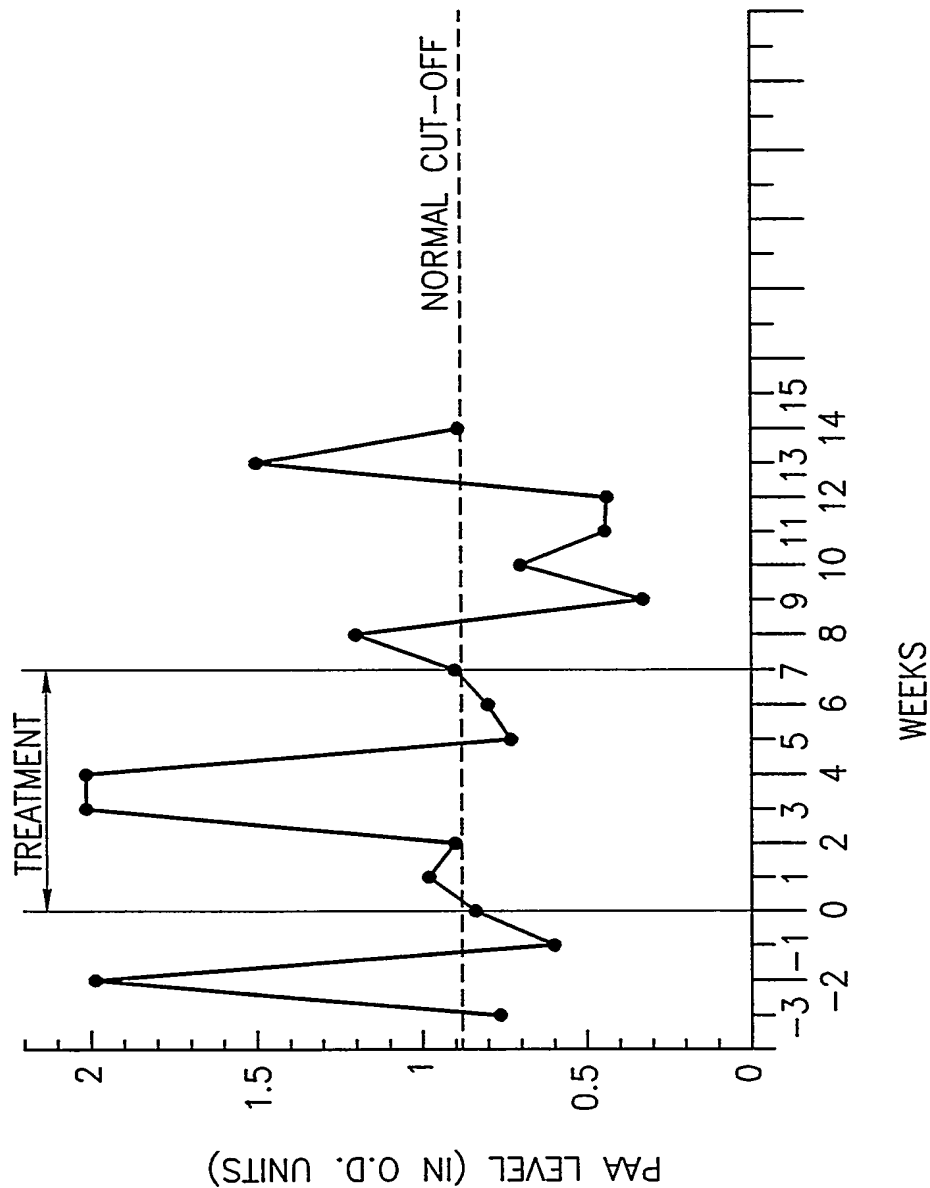
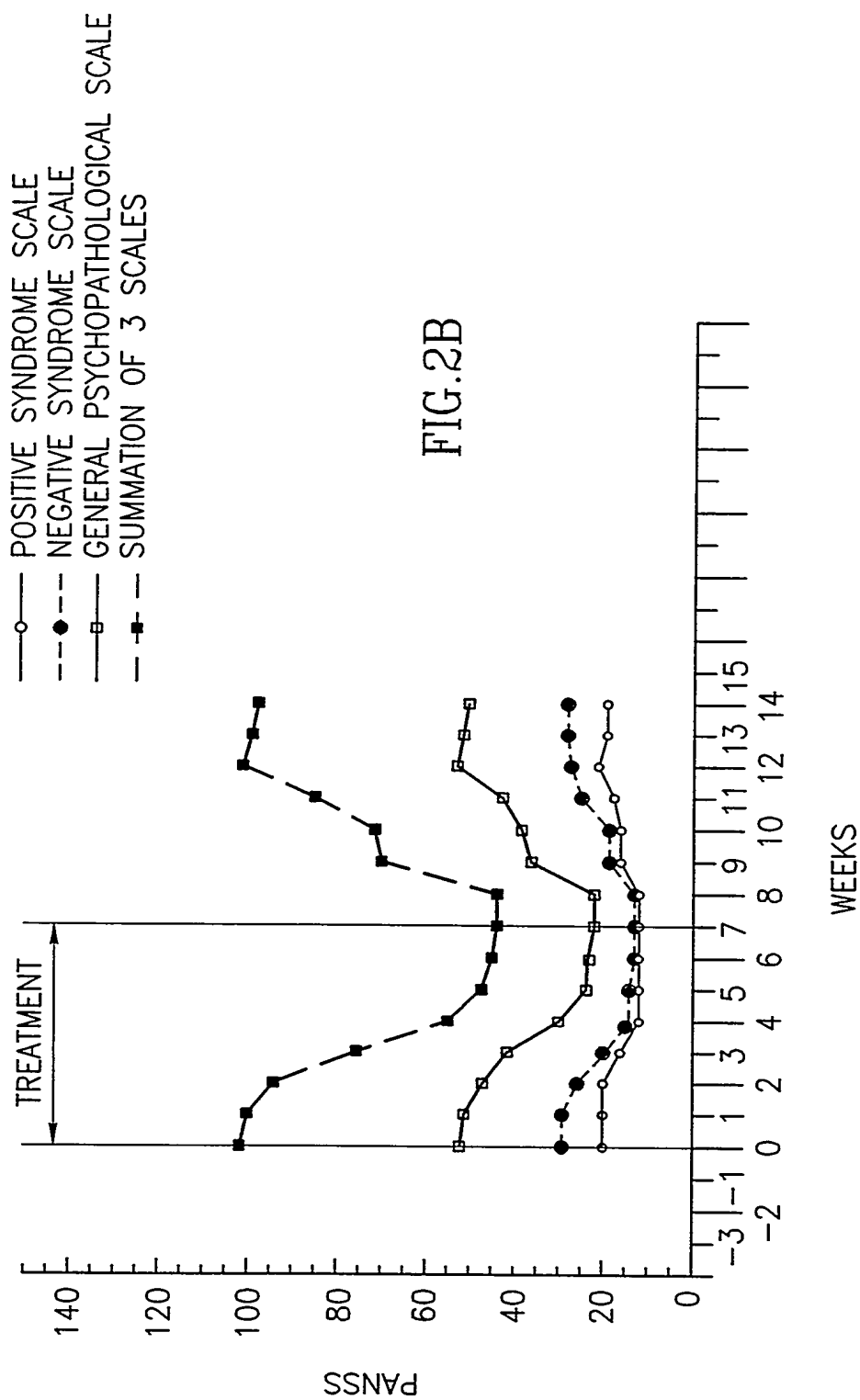


FIG.2A



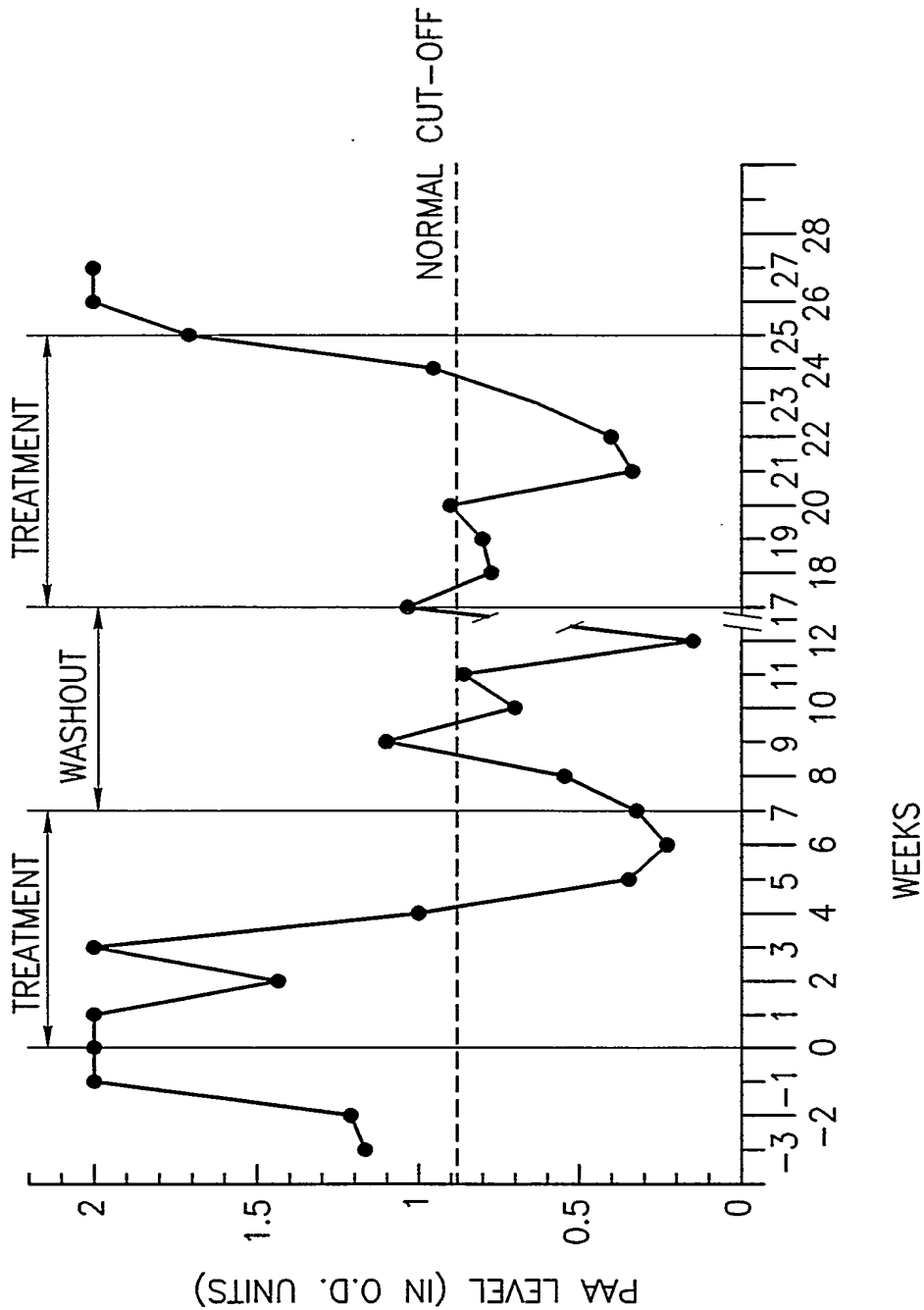


FIG.3A

—○— POSITIVE SYNDROME SCALE
- - -●- - - NEGATIVE SYNDROME SCALE
—□— GENERAL PSYCHOPATHOLOGICAL SCALE
- - -■- - - SUMMATION OF 3 SCALES

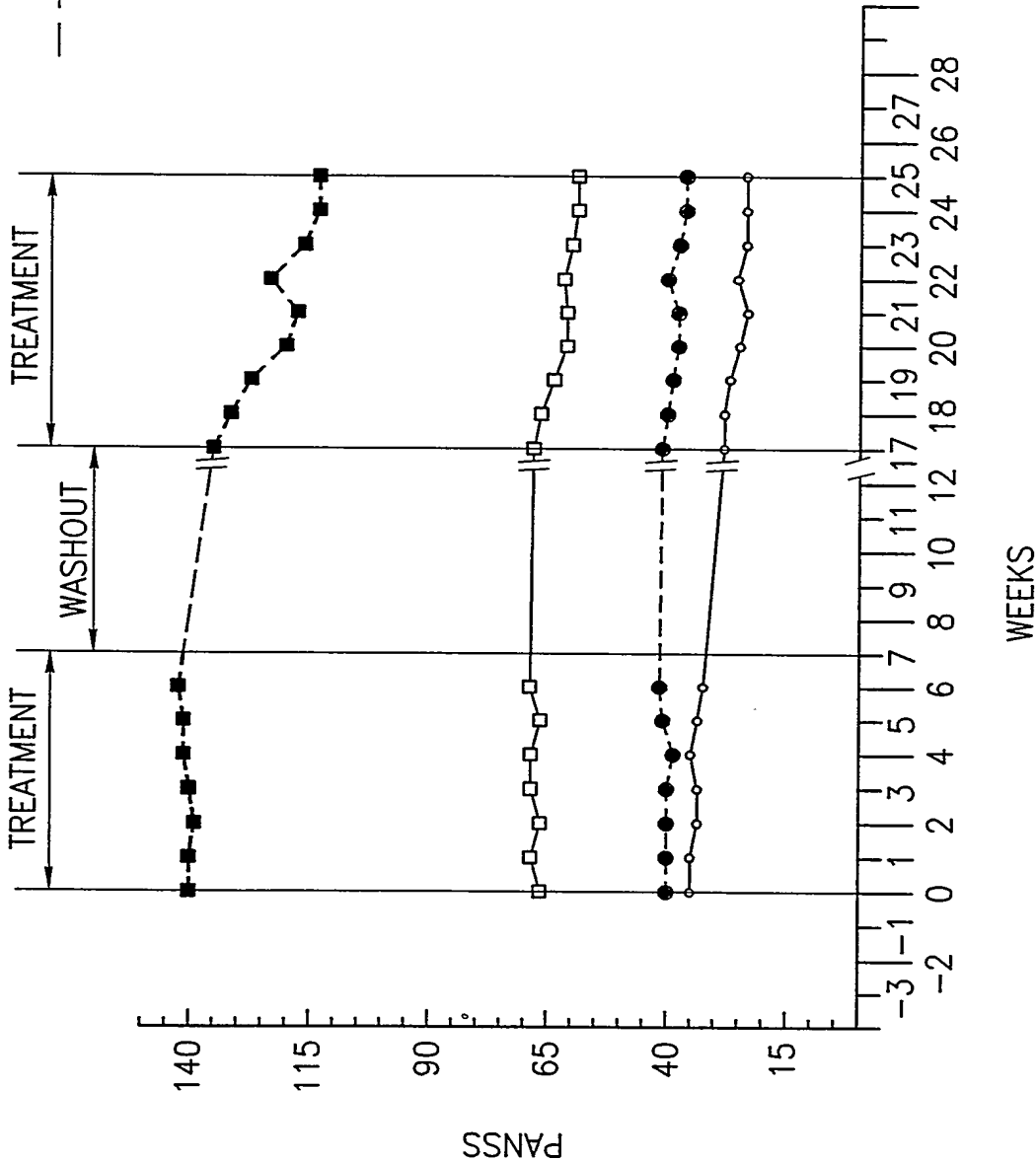


FIG.3B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/02289

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/57 A61K31/675 A61K38/13 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 16727 (UNIVERSITY COLLEGE LONDON) 2 September 1993 see the whole document especially page 1, line 16-18; page 3, line 1-4 & line 16-19 ---	1,4,7,11
X	PSYCHIATR. J. UNIV. OTTAWA, 1977, 2/3 (112-116), CANADA, GHADIRIAN A.M. 'Some recent advances in the study and treatment of schizophrenia in the Soviet Union' see page 115, column 1, line 35-50 --- -/--	1,2,4,5, 7,8,11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 September 1995

Date of mailing of the international search report

28.09.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

MAIR, J

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/EP 95/02289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LANCET, JUL 2 1994, 344 (8914) P59-60, ENGLAND, LEVINE J ET AL 'Treatment of schizophrenia with an immunosuppressant [letter] [published erratum appears in Lancet 1994 Jul 30;344(8918):346]' see the whole document ---	1-12
X	AUST. NEW ZEALAND J. PSYCHIATRY, 1985, 19/2 (184-188), AUSTRALIA, PRICE J. ET AL 'A case of cerebral systemic lupus erythematosus treated with methylprednisolone pulse therapy'	1,2
A	see the whole document ---	3-12
A	VOX SANG, 1983, 44 (2) P65-80, SWITZERLAND, VALBONESI M ET AL 'Plasma exchange in neurological diseases. A critical approach.' see page 74, column 2, line 5-30 see page 76, column 1, line 30 - page 77, column 1, line 15 ---	1-12
A	METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PSYCHIATRY, vol. 6, no. 7, 1984 pages 395-403, KNIGHT, J.G. 'Is schizophrenia an autoimmune disease?- a review' cited in the application see the whole document ---	1-12
A	PSYCHOBIOLOGY, vol. 21, no. 4, December 1993 pages 299-306, KESSLER, A. ET AL 'Platelets from schizophrenic patients bear autoimmune antibodies that inhibit dopamine uptake' cited in the application see the whole document ---	1-12
X	BUDAVARI, S. (ED.) 'THE MERCK INDEX' 1989 , MERCK & CO. INC., 11TH ED. , RAHWAY, N.J., U.S.A. see p. 431, compound no. 2759 & p. 1224, compound no. 7727 -----	1,2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 95/ 02289

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 7-12 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/02289

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9316727	02-09-93	AU-B- 3637793	13-09-93
		CA-A- 2130117	02-09-93
		CZ-A- 9402023	15-02-95
		EP-A- 0630259	28-12-94
		JP-T- 7506093	06-07-95
		NO-A- 943082	17-10-94
